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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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NEW ENGLAND BIOLABS, INC. 32 TOZER ROAD BEVERLY, MA 01915			SWITZER, JULIET CAROLINE	
		ART UNIT		PAPER NUMBER
				1634

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Supplemental
Office Action Summary

	Application No.	Applicant(s)
	09/701,626	RALEIGH ET AL.
Examiner	Art Unit	
Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 24 December 2003.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-14 and 17-20 is/are pending in the application.
- 4a) Of the above claim(s) 17 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-14 and 18-20 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) 1-14 and 17-20 are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date May 5 2003
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____

DETAILED ACTION

1. This office action is written in response to a telephonic interview held 11 May 2004 and mailed 14 May 2004, and in response to applicant's amendments and remarks filed 24 December 2003. All previous rejections are hereby WITHDRAWN in view of applicant's arguments set forth in the response. New grounds of rejection are set forth in this office action. This action is NON-FINAL.

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-14 and 18-20, drawn to methods for cloning prokaryotic genes and methods for identifying the presence of gene cassette arrays.

Group II, claim(s) 17, drawn to a method for identifying gene cassette arrays from a predetermined DNA sequence.

3. The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The invention of group I includes methods which rely on the manipulation (i.e. amplification, hybridization) of nucleic acids for the detection of gene cassette arrays in nucleic acid sample, in the end resulting in gene discovery or cassette detection. These are not joined by a special technical feature to the methods of group II which are directed towards identifying arrays in predetermined sequence by screening the sequence for known motifs, as exemplified in the specification by using computer data mining methods to accomplish the goals. There is a lack of unity of invention with regard to the required steps and with regard to the purpose of the methods set forth in the two different groups.

4. During a telephone conversation with Harriet Strumple on 11/7/04 a provisional election was made without traverse to prosecute the invention of group I, claims 1-14 and 18-20.

Art Unit: 1634

Affirmation of this election must be made by applicant in replying to this Office action. Claim 17 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 2, 3, 4, 5, 6, 18, 19, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite over the recitation “cloning one or more prokaryotic genes in a cassette array” because it is not clear if applicant intends to be cloning genes that are located in a cassette array in their natural form, for example into a vector, or if applicant intends to be cloning genes into a cassette array so that the final produce is within a “cassette array.” Claims 2, 3, 4, 5, 6, 18, 19, and 20 are also indefinite over this issue because they depend directly or indirectly from claim 1.

Claim 1 is further indefinite for the recitation “identified flanking repeat sequences” because it is not clear from the claim what the repeat sequences are flanking. Claims 2, 3, 4, 5,

6, 18, 19, and 20 are also indefinite over this issue because they depend directly or indirectly from claim 1.

Claim 2 is indefinite over the recitation “wherein the one or more genes are selected from the group of peptides consisting of” because genes are nucleic acids and not peptides, and therefore it is not clear how genes can be selected from a group of peptides. Claims 3, 4, 18, 19, and 20 are also indefinite over this issue because they depend from claim 1.

Claims 3 and 4 are indefinite because they recite the phrase “said diversity selected genes” which lacks antecedent basis in the claims.

Claim 7 is indefinite because it is not clear from the steps of the claim how the method steps set forth in (a) and (b) accomplish the goal of the preamble as set forth in the claim. The preamble recites a method for identifying the presence of gene cassette arrays, but the method steps conclude with detecting the presence of a stable hybrid. The claim does not set forth how the preamble is accomplished by the method steps, and therefore, it is not clear if the method is directed towards detecting cassette arrays or if the method is simply directed towards detecting any DNA hybrid with an oligonucleotide which hybridizes to any one or more of SEQ ID NO: 5-SEQ ID NO: 78. Claims 8-14 are also indefinite over this issue because they depend directly or indirectly from claim 7.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-6 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for cloning genes as recited in claim 1 which utilize primers that are fragments of instant SEQ ID NO: 5-SEQ ID NO: 78 for amplification of *P. alcaligenes* DNA, does not reasonably provide enablement for methods which use any additional oligonucleotide primers to identified flanking repeat sequences. Furthermore, while the specification is enabling for a screening method which isolated gene cassettes, the specification is not enabling for claims which recite the particular genes to be cloned.

Further, claims 7-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of detection of gene cassette arrays in *Pseudomonas* which utilize instant SEQ ID NO: 5- SEQ ID NO: 78 as primers or probes, or fragments of these sequences (as exemplified in claim 10) as primers or probes, the specification is not enabling for the use of any or all fragments that would hybridize under any conditions to these sequences. Furthermore, the specification is not enabling for the detection of gene cassette arrays in all *Pseudomonas* species or in any other genus of prokaryote.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the Invention

The claims 1-6 and 18-20 are drawn to methods for cloning one or more prokaryotic genes and include steps of hybridizing oligonucleotide primers to “identified” flanking repeat sequences in a cassette array, amplifying the DNA between the primers and ligating the fragments of step (b) into a vector for cloning the one or more genes. The claims specifically

Art Unit: 1634

recite a number of possibly types of genes that are isolated including, for example, restriction endonuclease genes, methyltransferase genes, fimbrial proteins, kinases, and drug resistance determinants. Thus, the nature of the invention is concerned with the isolation of coding sequences from within gene cassettes via amplification.

Claims 7-14 recite a method for identifying the presence of a gene cassette array from within a target DNA preparation said method comprising the steps of hybridizing at least one oligonucleotide which hybridizes to one or more of SEQ ID NO: 5 through SEQ ID NO: 78 to a DNA preparation and detecting the presence of a stable DNA-DNA hybrid. Ostensibly, the presence of the hybrid is an indicator of the presence of a gene cassette array, however, the claim does not provide a connection between the method as recited in the active steps and the preamble of the claims. Nonetheless, it appears that the nature of the invention for these claims requires a relationship between the hybridization oligonucleotide and the presence of a gene cassette array.

Scope of the invention

Claim 1 is broadly drawn to encompass the isolation of any gene from any species of prokaryote via amplification with primers to flanking repeat sequences. The primers to be used in the method are entirely undefined, other than the recitation that they are to “identified flanking repeat sequences in the cassette array.” The preamble of the claim defines the cassette array as “being characterized by a plurality of genes where each gene is embedded in a predictable nucleotide sequence including a repeat DNA sequence.” The meaning of this preamble is open to many different interpretations, and could include, for example, the amplification of sequences interspersed between any “predictable” repeats.

The specification discusses in particular integrons and superintegrons as mobile gene cassettes interspersed in prokaryote genomes. These structures have open reading frames which are separated by gene sequences which are classically referred to as 59-base pair elements in the prior art (see for example Mazel et al., p. 605, 3rd column). A preferred embodiment contemplated by applicants is an embodiment wherein the primers used in claim 1 hybridize within these elements and amplify the intervening sequence, which is expected to contain an open reading frame. The instant specification provides a large number of such sequences for only a single prokaryotic species, *Psuedomonas alcaligenes*. No gene cassette arrays or predictable repeat sequences are disclosed in the specification for any other species of *Psuedomonas* or for any other genus or prokaryote.

Claims 2, 3, 4, 18, 19, and 20 specifically recite a number of different types of proteins whose genes may be isolated using the claimed methods. However, there is no guidance or direction in the specification as to how to direct isolation so as to specifically obtain any one of these, as required by the claims. Even for *P. alcaligenes*, what type of gene is isolated by the instant method is entirely due to chance since it is entirely unpredictable as to what sequences will be located in the cassette structures. The specification does not provide any guidance as to how to particularly isolate any of the specifically recited gene types. The specification demonstrates that in *P. alcaligenes* a gene encoding the restriction enzyme PacI is embedded in a gene cassette, but the specification does not give any guidance as to the structure of the gene sequence or how it in particular may be cloned. Guidance is given in the specification as to how to screen for a number of different protein activities, but there is no way to predict a priori for

Art Unit: 1634

Pseudomonas species or for any prokaryote species what type of genes will be isolated using the claimed methods.

The scope of claims 7-14 is also quite broad in nature, owing to the fact that the method claim very broadly defines the oligonucleotide probe used in the assay as being one which “hybridizes to one or more of SEQ ID NO: 5 through SEQ ID NO: 78,” and that the claims encompass the detection of gene cassette arrays in any species of prokaryote. Thus, the claim includes the use of any nucleic acid that hybridizes under any conditions to form a stable hybrid with any portion of any one of these sequences. Though the preamble of the claim recites “A method for identifying the presence of gene cassette arrays,” there is no language in the body of the claim to even require that the oligonucleotide probe be specifically indicative of the presence of such arrays. Further, the specification does not specifically or clearly define what is meant by a “gene cassette array” and thus this language can be construed to mean the detection of any nucleic acid construct comprising a gene attached to any other gene, for example. The claim is not limited, for example, to detecting the presence of integron or integron-like structures.

Guidance provided in the specification

The specification hypothesizes that gene cassette arrays (of the integron type) may cluster genes related to pathogenicity and other biochemical functions. The specification provides general guidance as to the amplification and detection of cassette sequences, the cloning of genes, and the screening of genes for biological functions. The specification provides the nucleotide sequence of 73 sequences that were identified as Psuedomonas alcaligenes repeat (PAR) sequences that appear to be similar in structure to the 59-base pair elements present in integrons in other species (E. coli, for example). The specification does not, however, provide

Art Unit: 1634

any guidance as to the structure (i.e. nucleotide sequence) of additional repeat sequences from any other prokaryote species. The specification suggests that a large number of such sequences is necessary to enable the design of family specific primers (p. 16, first 3rd), and specification further teaches that individual members of the repeated array display imperfect dyad symmetry, making it very likely that PCR primer design will be complicated by hairpin formation or primer dimmers that will hinder amplification (p. 16, 2nd paragraph). The specification does not provide any guidance, however, as to how to overcome these obstacles for any or all species of prokaryotes, other the single species for which the practice of the claimed invention is exemplified.

Further, with regard to claims 7-14, the specification does not provide any guidance as to which portions of SEQ ID NO: 5 through SEQ ID NO: 78 are necessary for hybridization in order to in fact know that the formation of a specific hybrid is in fact indicative of a particular cassette array. This guidance is crucial given the breadth of the claims which include the use of any number of oligonucleotide probes that hybridize to only portions of the disclosed sequences. Absent any further guidance, it is highly unpredictable as to what sequences can be used to detect the gene cassette arrays in prokaryotes other than *Pseudomonas alcaligenes*.

State of the Prior Art

Applicant summarizes the state of the prior art in the specification when applicant teaches “it has been considered unlikely that these repeat sequences would enable acquisition of cassette-encoded genes by PCR because of the degeneracy of the sequences and the secondary structure encoded by them... (specification, p. 5, lines 29-32).” Even in light of this, however, Mazel et al. (as cited in the prior art rejections herein) do exemplify amplification of cassettes using primers

to the repeat regions in *V. cholerae*. However, at the time the invention was made, extensive sequence information concerning the repeats for other prokaryote species was not known. The absence of this information from the prior art is critical given the importance of this information for designing primers and probes for the practice of the claimed inventions.

Working Examples

Turning to the working examples in the specification, Example 1 (beginning on p. 32) discloses the isolation of the genes encoding the restriction enzymes *PacI* and *PmeI* from *Psuedomonas alcaligenes* and *P. mendocina*, respectively, using previously taught cloning methods (p. 32, lines 17-22). After cloning of the genes, the surrounding sequence was cloned from both species (p. 32, lines 30-33). Repetitive sequences common to both segments were identified by visual inspection (p. 33, lines 4-5). Additional sequence was isolated from *P. alcaligenes* and was sequenced (p. 33-34). These sequences are given in SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4. Following sequencing a computer search of the 59.4 kilobases of sequence was conducted for putative repeat regions. A set of elements identified by motif searching are given in SEQ ID NO: 5-SEQ ID NO: 78 (p. 36).

Following identification of the elements by motif searching, a Southern blot was carried out against chromosomal DNA of *P. alcaligenes* using hybridization probes SEQ ID NO: 80-83 (p. 37), and multiple fragments in each digest hybridized with the probes (see Figure 8), and applicant teaches that this hybridization indicates that the oligonucleotides represents a repeated sequence (p. 37, last sentence).

The specification provides discussion of a method for detecting cassette arrays in a population by using primers annealing to each end of the repeats separating the cassettes in a

Art Unit: 1634

PCR experiment, and validate this method using SEQ ID NO: 84 and 85 in six species of *Pseudomonas* (p. 39). Of the six different *Pseudomonas* species tested, two yielded multiple amplification products. Four of the species, therefore, did not yield products.

In example 2, applicants teach PCR amplification of *P. alcaligenes* DNA using primers SEQ ID NO: 86-91 and cloning of the cassettes contained therein (p. 46-47). Applicants further discusses methods of screening the cloned sequences for functional report and assessing clone identity, but these discussions are prophetic in nature (p. 47-51). Thus, the putative genes sequences within the PCR products were not detected. Further, applicants suggest that the cassettes “will encode many different sorts of genes (p. 43, line7),” but do not provide any examples of genes within the putative cassette arrays, other than the genes encoding the restriction enzymes PacI and PmeI.

Thus, the specification does not provide a single working example wherein the claimed method is actually practiced for any species other than *P. alcaligenes*. Further, though the amplification and cloning taught in example 2 is similar to that recited in claim 1, there is no subsequent analysis to determine if in fact the cloned nucleic acids are “genes,” which encode any known or unknown polypeptide.

Level of Unpredictability

The level of unpredictability with regard to practicing the claimed invention commensurate in scope with the claims is quite high.

For example, it is highly unpredictable as to which sequences can be used to amplify genes contained between repeat regions in cassette arrays for organisms other than Psuedomonas alcaligenes. This unpredictability is highlighted by the fact that primers designed based on the

sequences disclosed herein were able to produce amplification products in only two of six different *Pseudomonas* species tested (see p. 39). Indeed, this problem is further illustrated in the post-filing date art where Vaisvila et al. (*Molecular Microbiology*, 2001, 42(3)587-601) attempted to use primers based on *P. alcaligenes* repeats to amplify potential repeated regions in forty-seven different bacterial strains, and positive isolates belonged only to the genus *Pseudomonas* (p. 594), and of these, products were only amplified from three different species (see figure description 9b). Barker et al. (1994, *Journal of Bacteriology*, Vol. 176, No. 17) also demonstrate the highly specific nature of the sequence of the repeat elements in VCR, as they teach that a VCR specific probe hybridizes only to some *V. cholerae* species but no to other *Vibrio* species or to *Aeromonas* species tested (p. 5455).

Additional putative primer sequences that might be useful for amplifying different species of prokaryotes would have to be empirically determined, as no these sequences are entirely unpredictable. The specification further discusses the unpredictability and difficulty involved in the design of such primers. The specification teaches that these repeat sequences is that the members of a repeated array are degenerate, so that PCR primers hybridizing to most or all of the members are difficult to design, and that accordingly, a large number of such sequences is necessary to enable the design of family specific primers (p. 16, first 3rd). The specification further teaches that individual members of the repeated array display imperfect dyad symmetry, making it very likely that PCR primer design will be complicated by hairpin formation or primer dimmers that will hinder amplification (p. 16, 2nd paragraph). Each of these obstacles would have to be considered empirically for any given species of prokaryote, and so it would be necessary for any species of prokaryote to undertake extensive and unpredictable

Art Unit: 1634

experimentation in order to obtain the sequence information necessary to practice the claimed invention.

Furthermore, with regard to claims 2, 3, 4, 18, 19, and 20 which all require the isolation of particular types of genes, it would be highly unpredictable as to how to direct the amplification specifically to lead to the cloning of any of these genes, as it is unknown which of these genes are actually present within the cassette arrays in any or all prokaryote species. Barker et al. teach that eight sequenced ORFs from within *V. cholerae* gene cassettes had no significant similarity to known protein sequences (p. 5456, 1st column). The instant specification provides only speculation that these types genes may be identified within the cassette sequences. The claims require that they are located between repeat sequences, as the claims require the cloning of these types of genes. There is not a nexus between the showing in the specification and the instant claims.

Likewise, with regard to claims 7-14, the practice of the instant invention for the “identification of gene cassette arrays” is highly unpredictable due to the broad scope of the hybridization probes recited for use within claim 7 and the fact that the claims encompass detecting “gene cassette arrays” in any species of prokaryote using sequences that hybridize to portions of SEQ ID NO: 5 through SEQ ID NO: 78. The specification does not provide any guidance as to which portions of SEQ ID NO: 5 through SEQ ID NO: 78 are critical for the identification of gene cassette arrays, and the claims encompass the use of any nucleic acid that hybridizes under any possible conditions to the disclosed sequences.

Conclusion

Art Unit: 1634

Thus, in view of this analysis, namely in view of the broad scope of the claims, and the lack of commensurate examples or guidance, in view of the state of the prior art which does not fill the holes lacking in the disclosure, in view of the high level of unpredictability in this technology, as demonstrated and discussed in applicant's specification, it is concluded that it would require undue experimentation to practice the claimed invention commensurate in scope with the instantly pending claims.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Lorenz et al.

(Biochemistry and Molecular Biology International, pages 705-713, Vol. 36, No. 4, July 1995).

Lorenz et al. teach a method for cloning one or more prokaryotic genes, the method comprising the steps of

- (a) hybridizing oligonucleotide primers to identified flanking repeat sequences in the cassette array;
- (b) amplifying the DNA between the hybridized primers of step (a) to produce DNA fragments which contain one or more genes;
- (c) ligating the DNA fragments of step (b) into a vector for cloning the one or more genes in a host cell.

Lorenz et al. teach a method in which primers to repeat regions are used to amplify the sequence between the repeats. These are considered to be in a “cassette array” since the location of the genes is within the predictable sequence of the repeats, and there are multiple genes within the genome of the prokaryote Prochlorococcus that are arrayed within these repeats. Open reading frames were identified within the products amplified by the M13 and OPB-10 primers (see Table 2 and Table 3). The teaching of Lorenz et al. anticipated claim 1.

12. Claims 7 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US 5474796).

Brennan teaches a method comprising the steps of (a) hybridizing at least one oligonucleotide which hybridizes to one or more of SEQ ID NO: 5 through SEQ ID NO: 78 to a DNA preparation and (b) detecting the presence of a stable DNA-DNA hybrid. Namely, Brennan teaches the hybridization of a labeled probe with an array that comprises every possible 10-mer oligonucleotide and assessing the binding pattern (Col. 9-10, Example 4). This disclosure teaches each of the method steps of the instant claim, as the 10-mer array taught by Brennan would have many oligonucleotides that would hybridize to each of SEQ ID NO: 5 through SEQ ID NO: 78 since the array has all possible nucleotide sequences. Therefore, the claims are rejected in view of Brennan.

13. Claims 7, 11, and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Lansdorp (US 6514693).Claims 7, 11, and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Lansdorp (US 6514693).

Lansdorp teaches a method comprising the steps of (a) hybridizing at least one oligonucleotide which hybridizes to one or more of SEQ ID NO: 5 through SEQ ID NO: 78 to a

Art Unit: 1634

DNA preparation and (b) detecting the presence of a stable DNA-DNA hybrid. Namely, Lansdorp teaches a hybridization method using a probe having their SEQ ID NO: 6, this method comprising hybridizing the probe to a sample and detecting the stable hybrid (See Col. 5, for example). The probe SEQ ID NO: 6 taught by Lansdorp would hybridize to instant SEQ ID NO: 11, as this probe shares identity with nucleotides 58-71 of SEQ ID NO: 11, having only three mismatches over these 14 nucleotides at positions 61, 65, and 71 of the sequence. Thus, the teachings of Lansdorp provide methods which meet the limitations of the method steps of the instant claims. Lansdrop teach samples that are from humans, which are considered an individual strain. It is noted that in the instant claims it is not clear how the preamble of the claims would breathe life and meaning into the claims.

14. Claims 7, 8, 11, 12, 13, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Barker et al. (Journal of Bacteriology, Sept 1994; as cited in IDS).

Barker et al. teach a method for identifying the presence of gene cassette arrays from within a target DNA preparation comprising the steps of:

- (a) hybridizing at least one oligonucleotide which hybridizes to one or more of SEQ ID NO: 5 through SEQ ID NO: 78 to a DNA preparation; and
- (b) detecting the presence of a stable DNA-DNA hybrid.

Namely, Barker et al. teach southern hybridization of a VCR-specific probe to V. cholerae samples (p. 5454; Figure 4). This probe is considered to be an oligonucleotide which hybridizes to “one or more of SEQ ID NO: 5 through SEQ ID NO: 78” because the claim does not set forth any hybridization conditions or requirements, nor does the claim require that the probe hybridize to the full length of any of the specific sequences. The probe used by Barker et

Art Unit: 1634

al. would be expected to hybridize under very low stringency conditions to at least a portion of at least one of the sequences recited in the claims. Barker et al. test individual strains of *V. cholerae* (see figure 7 description), and test a group of strains, albeit each individually. The samples are considered "environmental samples" because this organism is present in the environment at least of the cell cultures.

15.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. Claims 1, 2, 5, and 6 rejected under 35 U.S.C. 103(a) as being unpatentable over Mazel et al. (Science, Vol. 280, April 1998) in view of Ogawa et al. (Micorbiol. Immunol., Vol. 37, No. 8, p. 607-616).

Mazel et al. teach a method of cloning one or more prokaryotic genes in a cassette array, the array being characterized by a plurality of genes where each gene is embedded in a predictable nucleotide sequence including a repeat DNA sequence, the method comprising the steps of:

(a) hybridizing oligonucleotide primers to identified flanking repeat sequences in the cassette array; and

(b) amplifying the DNA between the hybridized primers of step (a) to produce DNA fragments which contain one or more genes.

Specifically, turning to p. 607, Mazel et al. teach that *Vibrio* isolates were screened by means of oligonucleotide primers corresponding to the most conserved regions of the VCR sequences. The "VCR" sequences are DNA repeat sequences within the *Vibrio cholerae* genome. Mazel et al. teach that VCR cassettes were identified in 6 of the 7 isolates tested (see Table 2). Mazel et al. further teach that some of these cassettes were sequenced from *V. metschnikovii* PCR products (2nd column), including one that contained 67% identity with ORF5 from *V. cholerae*. With regard to claim 5, the VCR-2 primer used by Mazel et al. has within it two restriction sites.

Mazel et al. do not teach a step of (c) ligating the DNA fragments of step (b) into a vector for cloning the amplified genes into a host cell.

However, at the time the invention was made, it was routine to ligate a DNA fragment into vector prior to sequencing of the fragment. Likewise, it was routine to ligate sequences containing open reading frames into expression vectors for the purpose of further characterizing the unknown coding sequences. For example, Ogawa et al. teach the isolation of a coding sequence that is flanked by repeats from *V. cholerae*, cloning of the sequence into a vector (p. 608), and subsequent sequencing of the gene. It would have been *prima facie* obvious at the time the invention was made to have modified the methods taught by Mazel et al. so as to have included a step of cloning the amplified fragments into vectors for sequencing or for expression of the unknown ORF. One would have been motivated to undertake such a transformation in order to have further studied the uncharacterized open reading frame amplified from the *V. metschnikovii* genomic DNA. Therefore, in view of the teachings of Mazel et al. in view of Ogawa et al., the instant invention is *prima facie* obvious.

Conclusion

18. No claim is allowed.
19. Methods which require oligonucleotides that comprise instant SEQ ID NO: 79 through SEQ ID NO: 91 are free of the prior art as the prior art does not teach or suggest any of these molecules (for example, claim 11).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached by calling (571) 272-0745.

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Art Unit: 1634

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